



Original Article

The Effect of Bisoprolol on Heart Failure Preserved Ejection Fraction / Hfpef Patient's Quality Of Life

Ayu Asri Devi Adityawati^{1*}, Anna Fuji Rahimah^{1,2}, Mohammad Saifur Rohman^{1,2}, Setyasih Anjarwani^{1,2}, Djangan Sargowo^{1,2}

¹ Brawijaya Cardiovascular Research Center, Departement of Cardiology and Vascular Medicine, Faculty of medicine, Universitas Brawijaya, Malang, Indonesia

² Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya – dr. Saiful Anwar General Hospital, Malang, Indonesia.

ARTICLE INFO

Keywords:
Bisoprolol;
HFpEF;
QoL

ABSTRACT

Background: Global Public Health Burden of Heart Failure reported the growing prevalence of heart failure which is 64.3 million affected in 2020 worldwide with half of the case classified as Heart Failure Preserved Ejection Fraction (HFpEF). It is well known that someone who has been diagnosed with heart failure will have a poorer quality of life/QoL. β -blocker is a heart rate lowering agent with a potency to improve the patient's clinical outcomes, one of them is QoL.

Objective: This study aimed to observe and evaluate the effect of bisoprolol, a type of β -blocker, in the improvement of HFpEF patient's QoL.

Method: This study is a retrospective cohort following HFpEF patients who received bisoprolol and HFpEF patients who did not receive bisoprolol. The study participants were selected using purposive sampling method.

Result: Our study found that from all HFpEF patients who received bisoprolol 102 patients had a good QoL and 2 patients had a poor QoL ($p=0.000$) according to Minnesota Living With Heart Failure Questionnaire (MLHFQ). The median physical score in the patient who did not receive bisoprolol was 10 while the median score of the patient who received β -blocker was 4 ($p=0.000$). The mean emotional score for the patients who did not receive β -blocker was 3 while the mean score of the patients who received β -blocker was 1 ($p=0.000$).

Conclusion: We conclude that the use of bisoprolol could improve the HFpEF patient's QoL evaluated by total score, physical score, and emotional score.

1. Introduction

Global Public Health Burden of Heart Failure reported that there was an increasing prevalence of heart failure from 26 million people affected in 2017 to 64.3 million people worldwide in 2020 with half of the case classified as heart failure preserved ejection fraction/HFpEF1. Heart failure preserved ejection fraction or shortened as HFpEF is one of heart failure classification in which the ejection fraction is $>50\%$ based on European Society of Cardiology/ESC 2016 guideline for diagnosis and treatment of acute and chronic heart failure2. Patients with HFpEF are older and highly symptomatic with a poor QoL3. Because of that condition, the challenge to achieve our goals in treating HF patients must be face it, which are to improve their clinical status, functional capacity, and quality of life, prevent hospital admission and reduce mortality.2

Beta blocker/ β -blocker is a heart rate lowering agent that may increase the clinical outcome of heart failure patients.4 ESC 2016 guideline for diagnosis and treatment of acute and chronic heart failure stated the usage of β -blocker as a first-line recommendation therapy combined with ACE inhibitor.2 One of the most important outcomes that should be evaluated and become the main goal of therapy as we

know above is the patient's quality of life/QoL2 The Cardiac Insufficiency Bisoprolol Study in Elderly/CIBIS-ELD stated an increase in the quality of life from uptitration of β -blocker in patients with heart failure.5 Besides showing the effect of β -blocker uptitration on the quality of life, the study also evaluates the effect of β -blocker uptitration on the clinical variable such as heart rate where they found a reduction in the heart rate at the end of the study.5 Based on this fact, we think that there should be a study to observe and evaluate the effect of β -blocker such as bisoprolol on the quality of life of HFpEF patients.

2. Methods

Our study was a retrospective cohort performed in Saiful Anwar Hospital, Malang from April to July 2021. HFpEF patients data who were treated with bisoprolol and HFpEF patients who did not receive bisoprolol were collected according to the medical record. We used purposive sampling method with inclusion criteria consisted of: (1) age 30-75 years old diagnosed with heart failure based on the definition stated in the 2016 ESC guideline; (2) echocardiography criteria of LV EF $\geq 50\%$; (3) H2FPEF score confirmed as an HFpEF; (4) confirmed as a patient in Saiful Anwar Hospital; (5) signed informed

*Corresponding author at: Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
E-mail address: ayudevi@gmail.com (A. A. D. Adityawati).

<https://doi.org/10.21776/ub.hsj.2021.002.04.6>

Received 9 July 2021; Received in revised form 30 July 2021; Accepted 15 August 2021

Available online 30 October 2021

2214-5400/ ©UB Press. All rights reserved.

consent to participate in the research. The exclusion criteria were (1) patient died before the study interview (2) patient was waiting for the procedure such as cardiac surgery, pacemaker implantation, CABG or heart transplant (3) patient was in a state of severe emotional stress based on a psychiatric diagnosis from medical record data; (4) patient with chronic diseases such as chronic kidney disease or pulmonary hypertension

The categorical variables were analyzed using Chi-square and all continuous variables were analyzed by T-test for data with normal distribution or Mann-Whitney for data not normally distributed. The confidence interval used in this study is 95% ($\alpha=0.05$).

3. Results

Our study followed 217 patients with 22 patients categorized as poor QoL and 195 patients categorized as good QoL (Table 1). Based on the data analysis, there were statistically significant differences in the QoL on some characteristics including HT ($p=0.004$), heart rate

($p=0.000$), and SBP ($p=0.000$). Other sample characteristics such as gender ($p=0.510$), age ($p=0.029$), DM ($p=0.365$), ischemic ($p=0.121$), smoker ($p=0.221$), height ($p=0.135$), weight ($p=0.071$), BMI ($p=0.502$), NYHA ($p=0.401$), EF ($p=0.721$), LAVI ($p=0.151$), TAPSE ($p=0.486$), E/A ($p=0.573$) and PCWP ($p=0.365$) did not show a significant difference.

Table 2 summarized the difference in the QoL between the patient who received bisoprolol and the patient who did not receive β -blocker. We found that 102 patients who received bisoprolol had a good QoL meanwhile 2 other patients who also received bisoprolol had a poor QoL. In the group that did not receive bisoprolol, 93 patients had a good QoL and 20 patients had poor QoL. The mean comparison of bisoprolol (2 categories) showed a p-value of 0.000 ($p<0.005$) which meant a statistically significant difference of the β -blocker usage in the quality of life. We also found the odds ratio/OR=10.97 which meant that the patients who received bisoprolol had a higher odds of 10.97 times to have a good QoL (CI 95%: 2.49-48.2).

Table 1. Sample Characteristics

| | | Poor QoL (n=22) | | Good QoL (n=195) | | p value |
|-------------------------|---------------|------------------|-----|---------------------|------|---------|
| | | F | % | F | % | |
| Gender ^F | L | 13 | 6 | 100 | 46.1 | 0.510 |
| | P | 9 | 4.1 | 95 | 43.8 | |
| Age ^t | Mean \pm SD | 63.41 \pm 9.34 | | 57.73 \pm 12.18 | | 0.029 |
| HT ^F | No | 2 | 9 | 77 | 35.5 | 0.004 |
| | Yes | 20 | 9.2 | 118 | 54.4 | |
| DM ^F | No | 17 | 7.8 | 165 | 76.0 | 0.365 |
| | Yes | 5 | 2.3 | 30 | 13.8 | |
| Ischemic ^F | No | 7 | 3.2 | 97 | 44.7 | 0.121 |
| | Yes | 15 | 6.9 | 98 | 45.2 | |
| Smoking ^F | No | 16 | 7.4 | 165 | 76.0 | 0.221 |
| | Yes | 6 | 2.8 | 30 | 13.8 | |
| Height ^M | (Median) | 163 | | 160 | | 0.135 |
| Weight ^M | (Median) | 69 | | 63 | | 0.071 |
| BMI ^t | Mean \pm SD | 25.4 \pm 3.39 | | 24.88 \pm 3.36 | | 0.502 |
| BMI ^C | Underweight | 0 | 0 | 3 | 0.9 | 0.829 |
| | Normal | 5 | 2.3 | 54 | 21.2 | |
| | overweight | 6 | 2.8 | 52 | 17.1 | |
| | Obesity 1 | 10 | 4.6 | 69 | 21.7 | |
| | Obesity 2 | 1 | 0.5 | 17 | 7.4 | |
| Heart Rate ^t | Mean \pm SD | 79.09 \pm 6.15 | | 73.27 \pm 7.18 | | 0.000 |

| | | | | | | |
|---------------------------|----------|---------------|-------|---------------|--------|-------|
| SBP ^M | (Median) | 132 (110-160) | | 122 (100-165) | | 0.000 |
| DBP ^M | (Median) | 80 (65-110) | | 80 (51-115) | | 0.078 |
| NYHA ^C | 1 | 14 | 6.5 | 125 | 57.6 | 0.401 |
| | 2 | 7 | 3.2 | 68 | 31.3 | |
| | 3 | 1 | 0.5 | 2 | 0.9 | |
| Total H2FPEF ^C | 2 | 9 | 4.12% | 65 | 29.81% | 0.774 |
| | 3 | 8 | 3.66% | 72 | 22.02% | |
| | 4 | 2 | 0.91% | 45 | 20.64% | |
| | 5 | 1 | 0.45 | 9 | 4.12% | |
| | 6 | 2 | 0.91% | 4 | 1.83% | |
| LAVI ^M | (Median) | 24.5 | | 27.95 | | 0.151 |
| TAPSE ^t | Mean±SD | 2.065±0.32 | | 2.006±0.388 | | 0.486 |
| E/A ^M | (Median) | 0.8 | | 0.9 | | 0.573 |
| PCWP ^M | (Median) | 16.05 (15-47) | | 16.0 (11-36) | | 0.365 |

Note: ^F = Fisher exact test; ^C = Chi square test; ^t = T test; ^M = Mann Whitney Test

QoL = Quality of Life; HT = Hypertension; DM = Diabetes Mellitus; BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; NYHA = New York Heart Association; LAVI = Left Atrial Volume Index; TAPSE = Tricuspid Annular Plane Systolic Excursion; PCWP = Pulmonary Capillary Wedge Pressure

Table 2. Mean Comparison of β -blocker to Total Score

| | | Poor QoL (n=22) | | Good QoL (n=195) | | p-value | CI 95% |
|------------|-----|-----------------|-----|------------------|------|---------|-----------|
| | | f | % | F | % | (OR) | |
| Bisoprolol | No | 20 | 9.2 | 93 | 42.9 | 0.000 | 2.49-48.2 |
| | Yes | 2 | 0.9 | 102 | 47.6 | (10.97) | |

Note:

QoL = Quality of Life; CI = Confidence Interval; OR = Odds Ratio

Based on Table 3, the median physical score from patients who did not receive bisoprolol was ten meanwhile the median score from patients who received bisoprolol was four. Statistical analysis with Mann-Whitney showed a significance of 0.000 ($p < 0.05$). This showed that the mean physical score of patients who did not receive bisoprolol and patients who received bisoprolol differed significantly. Our study also found the median emotional score of patients who did not receive bisoprolol was three. In the meantime, the median emotional score from patients who received bisoprolol was one. Statistical analysis with Mann-Whitney showed a p-value of 0.000 ($p < 0.05$) which meant there was a significant difference in mean emotional score in the patient who did not receive bisoprolol and patients who received bisoprolol, with a lower score in the patient who received bisoprolol according to MLHFQ.

4. Discussion

HFpEF is a heterogeneous syndrome accompanied by a variety of risk factors that contribute to the development of the condition which includes hypertension, obesity, diabetes mellitus,

coronary heart disease, valvular heart disease, atrial fibrillation, obstructive pulmonary disease, chronic kidney disease, and anemia.^{6,7}

We found that hypertension had a significant influence on the QoL in both groups, patients treated with bisoprolol and not treated with bisoprolol ($p = 0.004$). HFpEF patients without any history of hypertension in our study mostly exhibited a good QoL. Literature shows a negative correlation between hypertension and QoL, when the patient has a history of hypertension or severe hypertension, the QoL will be lower.⁸ Our study did not act in accordance with this negative correlation because in our study 118 patients with hypertension had a good QoL meanwhile only 20 patients with hypertension had a poor QoL. This might be influenced by a good blood pressure control done by the patient, as mentioned in Lee et al study in which the improvement of quality of life could have an effect on blood pressure control.⁸

Heart rate evaluation is among the most studied variable because of its relation with the clinical outcome of a patient with cardiovascular disease, as the study from O'Neal et al who concluded

Table 3. Mean Comparison of β -blocker to Physical Score and Emotional Score

| | Without Bisoprolol (n=113) | | | Bisoprolol (n=113) | | | p-value |
|-----------------|----------------------------|---------|-------------------|--------------------|---------|-----------------|---------|
| | Median | Min-max | Mean \pm SD | Median | Min-max | Mean \pm SD | |
| Physical score | 10 | (0-53) | 13.84 \pm 11.01 | 4 | (0-24) | 5.94 \pm 4.95 | 0.000 |
| Emotional score | 3 | (0-36) | 6.02 \pm 6.61 | 1 | (0-12) | 1.83 \pm 2.16 | 0.000 |

Note:

SD = Standard Deviation

that greater count of heart rate at rest is a factor that influences the clinical outcome in the HFpEF patient.⁹ Our study found that patients who had fewer heartbeats per minute mostly had a good QoL while patients with greater heartbeats per minute had a poor QoL. An increase in heart rate by 5-10 beats per minute will increase the mortality risk in the general mortality or mortality related to cardiovascular and also in the risk of hospitalization in the heart failure patient such as HFpEF patient, which is this finding had a great effect on the patient's QoL.¹⁰ An increase in the heart rate, reflects the increase in energy cost, activation of the sympathetic system, and excretion of catecholamines in heart failure patients. The upsurge of catecholamines in HFpEF patients might be accountable for a poorer outcome in patients with HFpEF both physically and psychologically.¹¹ There are some neurotransmitters that have an effect on someone's mood that will also affect the QoL at the end.¹¹ An increase in the heart rate facilitated by activation of the sympathetic system can also affect the blood pressure and initiate an upsurge in catecholamines as compensation. This can lead to a change in the patient's physical and psychological state.

Evaluation of the QoL by MLHFQ categorized 102 patients who received bisoprolol into a good QoL (47,0%). From the Fisher exact test, we found $p=0.000$ ($p<0.05$) which meant there was a significant difference in the QoL between the patient who received bisoprolol and the patient who did not receive bisoprolol. In our study, the patient who did not receive bisoprolol mostly had a poor QoL. This finding was supported by CIBIS ELD who found that the dose up-titration of β -blocker could improve the HFpEF patient's QoL evaluated by the SF-36 questionnaire.^{5,12} Kojima also had a similar discovery, he found that the use of β -blocker affects the QoL in a span of one year.¹³ We hope that the improvement of HFpEF patient's QoL when treated by β -blocker, like we found in our study, could give a new insight into the management of HFpEF even though there was still a big dispute.¹⁴

In the progression of heart failure, there is a hyperactivation of the sympathetic system, which manifest as an increase in the heart rate and an increase in the stimulation of β -adrenergic receptor at cardiomyocytes result an activation of Beta1AR-stimulating G (Gs) protein-adenylate cyclase-cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA).¹⁵ In the chronic condition, this can lead to persistent stimulation of β 1-adrenergic receptor which result in cardiomyocytes apoptosis, hypertrophy, and also fibrosis of the heart. B-blocker has a therapeutic role in the pathophysiology of HFpEF where it can lower the sympathetic system activation and hope to inhibit the persistent stimulation of β 1-adrenergic receptor¹⁵ and inhibit the delay of left ventricle relaxation as the result of the heart's inflexibility that can lead to an increase in diastolic filling pressure of the ventricle and reduction of the cardiac output.¹⁶

Another beneficial effect of beta blocker is the direct protection of myocardial from catecholamine toxicity. When HFpEF patients experience a reduction of cardiac output, the body will try to compensate for it by doing a counter-regulation. One mechanism is by increasing the regulation effect of the sympathetic system, unfortunately, this

can lead to the disruption of baroreceptor reflex¹⁷ and the over secretion of catecholamines¹⁸. Catecholamine (including dopamine, epinephrine, and norepinephrine) is an important stress response of the body that could be activated by an emotional response such as anxiety or fear¹¹. This discovery leads to a more holistic approach to HFpEF management in the hope to suppress the secretion of catecholamines. Prolonged catecholamine exposure could worsen the physical and psychological outcome of the patient that could result in a change of mood and a worse QoL in the patient with HFpEF.¹⁹

β -blocker can also act as an anti-remodeling in the HFpEF patient. Structurally, there is a difference in the remodeling process of HFpEF and other heart failures.²⁰ In HFpEF, the heart underwent concentric hypertrophy of the left ventricle even though some of the patients still have a normal left ventricle geometry.²¹ The use of β -blocker in the past study showed its role as a cardiac antiremodelling although the underlying mechanism was still unclear. The suggested mechanism was a reduction of left ventricle sphericity and functional regurgitation of the mitral.²² We should all keep in mind that almost all past studies of the heart failure patient had given the patient ACE-inhibitor before the administration of β -blocker which meant that the anti-remodeling effect was significantly influenced by the use of ACE-inhibitor and we could not estimate the same result if we eliminate the use of ACE-inhibitor.²³

5. Conclusion

Bisoprolol could improve the quality of life (total score, physical score, and emotional score) of HFpEF patients compared to a patient who did not receive bisoprolol.

6. Declarations

6.1. Ethics Approval and Consent to participate

This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

6.2. Consent for publication

Not applicable.

6.3. Availability of data and materials

Data used in our study were presented in the main text.

6.4. Competing interests

Not applicable.

6.5. Funding source

Not applicable.

6.6. Authors contributions

Idea/concept: MSR. Design: AADA. Control/supervision: AFR, MSR, SA, DS. Data collection/processing: AADA. Analysis/interpretation: AADA. Literature review: AFR, MSR. Writing the article: AADA. Critical review: AFR, MSR, SA, DS. Reviewed and approved the final draft and

are responsible for the content and similarity index of the manuscript.

6.7. Acknowledgements

We thank to Brawijaya Cardiovascular Research Center.

References

1. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev.* 2017;3(1):7-11. doi:10.15420/cfr.2016:25:2
2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2016;37(27):2129-2200m. doi:10.1093/eurheartj/ehw128
3. Fukuta H, Goto T, Wakami K, Ohte N. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. *Eur J Prev Cardiol.* 2016;23(1):78-85. doi:10.1177/2047487314564729
4. Kapoor JR, Heidenreich PA. Heart rate predicts mortality in patients with heart failure and preserved systolic function. *J Card Fail.* 2010;16(10):806-811. doi:10.1016/j.cardfail.2010.04.013
5. Chavanon M-L, Inkrot S, Zelenak C, et al. Regional differences in health-related quality of life in elderly heart failure patients: results from the CIBIS-ELD trial. *Clin Res Cardiol.* 2017;106(8):645-655. doi:10.1007/s00392-017-1101-6
6. Henning RJ. Diagnosis and treatment of heart failure with preserved left ventricular ejection fraction. *World J Cardiol.* 2020;12(1):7-25. doi:10.4330/wjc.v12.i1.7
7. Silverman DN, Shah SJ. Treatment of Heart Failure With Preserved Ejection Fraction (HFpEF): the Phenotype-Guided Approach. *Curr Treat Options Cardiovasc Med.* 2019;21(4). doi:10.1007/s11936-019-0709-4
8. Lee CJ, Park WJ, Suh JW, et al. Relationship between health-related quality of life and blood pressure control in patients with uncontrolled hypertension. *J Clin Hypertens.* 2020;22(8):1415-1424. doi:10.1111/jch.13941
9. O'Neal WT, Sandesara P, Hammadah M, et al. Gender Differences in the Risk of Adverse Outcomes in Patients With Atrial Fibrillation and Heart Failure With Preserved Ejection Fraction. *Am J Cardiol.* 2017;119(11):1785-1790. doi:10.1016/j.amjcard.2017.02.045
10. Shang X, Lu R, Liu M, Xiao S, Dong N. Heart rate and outcomes in patients with heart failure with preserved ejection fraction: A dose-response meta-analysis. *Medicine (Baltimore).* 2017;96(43):e8431. doi:10.1097/MD.00000000000008431
11. Scott E. All About Catecholamine in The Stress Response. The Spurge. Published 2021. Accessed June 5, 2021. <https://www.verywellmind.com/all-about-catecholamines-3145098>
12. Edelmann F, Musial-Bright L, Gelbrich G, et al. Tolerability and Feasibility of Beta-Blocker Titration in HFpEF Versus HFrEF: Insights From the CIBIS-ELD Trial. *JACC Heart Fail.* 2016;4(2):140-149. doi:10.1016/j.jchf.2015.10.008
13. Kojima T. The Effect of Beta Blockers on Maintaining Quality of Life at One Year After Discharge in Patients With Heart Failure With Preserved Ejection Fraction-From the Pursuit Hfpef Registry. *Circulation.* Published online 2019;140.Suppl 1: A12936-A12936. https://www.ahajournals.org/doi/abs/10.1161/circ.140.suppl_1.12936
14. Liu F, Chen Y, Feng X, Teng Z, Yuan Y, Bin J. Effects of beta-blockers on heart failure with preserved ejection fraction: a meta-analysis. *PLoS One.* 2014;9(3):e90555. doi:10.1371/journal.pone.0090555
15. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev.* 2017;3(1):7-11. doi:10.15420/cfr.2016:25:2
16. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2016;37(27):2129-2200m. doi:10.1093/eurheartj/ehw128
17. Fukuta H, Goto T, Wakami K, Ohte N. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. *Eur J Prev Cardiol.* 2016;23(1):78-85. doi:10.1177/2047487314564729
18. Kapoor JR, Heidenreich PA. Heart rate predicts mortality in patients with heart failure and preserved systolic function. *J Card Fail.* 2010;16(10):806-811. doi:10.1016/j.cardfail.2010.04.013
19. Chavanon M-L, Inkrot S, Zelenak C, et al. Regional differences in health-related quality of life in elderly heart failure patients: results from the CIBIS-ELD trial. *Clin Res Cardiol.* 2017;106(8):645-655. doi:10.1007/s00392-017-1101-6
20. Henning RJ. Diagnosis and treatment of heart failure with preserved left ventricular ejection fraction. *World J Cardiol.* 2020;12(1):7-25. doi:10.4330/wjc.v12.i1.7
21. Silverman DN, Shah SJ. Treatment of Heart Failure With Preserved Ejection Fraction (HFpEF): the Phenotype-Guided Approach. *Curr Treat Options Cardiovasc Med.* 2019;21(4). doi:10.1007/s11936-019-0709-4
22. Lee CJ, Park WJ, Suh JW, et al. Relationship between health-related quality of life and blood pressure control in patients with uncontrolled hypertension. *J Clin Hypertens.* 2020;22(8):1415-1424. doi:10.1111/jch.13941
23. O'Neal WT, Sandesara P, Hammadah M, et al. Gender Differences in the Risk of Adverse Outcomes in Patients With Atrial Fibrillation and Heart Failure With Preserved Ejection Fraction. *Am J Cardiol.* 2017;119(11):1785-1790. doi:10.1016/j.amjcard.2017.02.045
24. Shang X, Lu R, Liu M, Xiao S, Dong N. Heart rate and outcomes in patients with heart failure with preserved ejection fraction: A dose-response meta-analysis. *Medicine (Baltimore).* 2017;96(43):e8431. doi:10.1097/MD.00000000000008431
25. Scott E. All About Catecholamine in The Stress Response. The Spurge. Published 2021. Accessed June 5, 2021. <https://www.verywellmind.com/all-about-catecholamines-3145098>
26. Edelmann F, Musial-Bright L, Gelbrich G, et al. Tolerability and Feasibility of Beta-Blocker Titration in HFpEF Versus HFrEF: Insights From the CIBIS-ELD Trial. *JACC Heart Fail.* 2016;4(2):140-149. doi:10.1016/j.jchf.2015.10.008
27. Kojima T. The Effect of Beta Blockers on Maintaining Quality of Life at One Year After Discharge in Patients With Heart Failure With Preserved Ejection Fraction-From the Pursuit Hfpef Registry. *Circulation.* Published online 2019;140.Suppl 1: A12936-A12936. https://www.ahajournals.org/doi/abs/10.1161/circ.140.suppl_1.12936
28. Liu F, Chen Y, Feng X, Teng Z, Yuan Y, Bin J. Effects of beta-blockers on heart failure with preserved ejection fraction: a meta-analysis. *PLoS One.* 2014;9(3):e90555. doi:10.1371/journal.pone.0090555
29. Xu X, Wang DW. The progress and controversial of the use of beta blockers in patients with heart failure with a preserved ejection fraction. *IJC Hear Vasc.* 2020;26:100451. doi:10.1016/j.ijcha.2019.100451

29. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med.* 2004;350(19):1953-1959. doi:10.1056/NEJMoa032566
30. Ahmad SS, Gerson MC. Sympathetic drive stimulating diastolic dysfunction? *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol.* 2018;25(4):1110-1113. doi:10.1007/s12350-017-0809-z
31. Borovac JA, D'Amario D, Bozic J, Glavas D. Sympathetic nervous system activation and heart failure: Current state of evidence and the pathophysiology in the light of novel biomarkers. *World J Cardiol.* 2020;12(8):373-408. doi:10.4330/wjc.v12.i8.373
32. Goldstein DS, Eisenhofer G, Kopin IJ. Sources and significance of plasma levels of catechols and their metabolites in humans. *J Pharmacol Exp Ther.* 2003;305(3):800-811. doi:10.1124/jpet.103.049270
33. Ma C, Luo H, Fan L, Liu X, Gao C. Heart failure with preserved ejection fraction: an update on pathophysiology, diagnosis, treatment, and prognosis. *Brazilian J Med Biol Res = Rev Bras Pesqui medicas e Biol.* 2020;53(7):e9646. doi:10.1590/1414-431X20209646
34. Pfeffer MA, Shah AM, Borlaug BA. Heart Failure with Preserved Ejection Fraction in Perspective. *Circ Res.* 2019;124(11):1598-1617. doi:10.1161/CIRCRESAHA.119.313572
35. Xie M, Burchfield JS, Hill JA. Pathological ventricular remodeling: therapies: part 2 of 2. *Circulation.* 2013;128(9):1021-1030. doi:10.1161/CIRCULATIONAHA.113.001879
36. Frigerio M, Roubina E. Drugs for left ventricular remodeling in heart failure. *Am J Cardiol.* 2005;96(12A):10L-18L. doi:10.1016/j.amjcard.2005.09.060